JAMA Oncology | Original Investigation

Therapeutic Options for Neuroendocrine Tumors
A Systematic Review and Network Meta-analysis

Reto M. Kaderli, MD; Marko Spanjol, MD; Attila Kollár, MD; Lukas Bütikofer, PhD; Viktoria Gloy, PhD; Rebecca A. Dumont, MD; Christian A. Seiler, MD; Emanuel R. Christ, MD, PhD; Piotr Radojewski, MD; Matthias Briel, MD; Martin A. Walter, MD

IMPORTANCE Multiple therapies are currently available for patients with neuroendocrine tumors (NETs), yet many therapies have not been compared head-to-head within randomized clinical trials (RCTs).

OBJECTIVE To assess the relative safety and efficacy of therapies for NETs.

DATA SOURCES PubMed, Embase, the Cochrane Central Register of Controlled Trials, trial registries, meeting abstracts, and reference lists from January 1, 1947, to March 2, 2018, were searched. Key search terms included *neuroendocrine tumors*, *gastrointestinal neoplasms*, *therapy*, and *randomized controlled trial*.

STUDY SELECTION Randomized clinical trials comparing 2 or more therapies in patients with NETs (primarily gastrointestinal and pancreatic) were evaluated. Thirty RCTs met the selection criteria.

DATA EXTRACTION AND SYNTHESIS Pairs of independent reviewers screened studies, extracted data, and assessed the risk of bias. A network meta-analysis with a frequentist approach was used to compare the efficacy of therapies; the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline was used.

MAIN OUTCOMES AND MEASURES Disease control, progression-free survival, overall survival, adverse events, and quality of life.

RESULTS The systematic review identified 30 relevant RCTs comprising 3895 patients (48.4% women) assigned to 22 different therapies for NETs. These therapies showed a broad range of risk for serious and nonserious adverse events. The network meta-analyses included 16 RCTs with predominantly a low risk of bias; nevertheless, precision-of-treatment estimates and estimated heterogeneity were limited. The network meta-analysis found 7 therapies for pancreatic NETs: everolimus (hazard ratio [HR], 0.35 [95% CI, 0.28-0.45]), everolimus plus somatostatin analogue (HR, 0.35 [95% CI, 0.25-0.51]), everolimus plus bevacizumab plus somatostatin analogue (HR, 0.44 [95% CI, 0.26-0.75]), interferon (HR, 0.37 [95% CI, 0.16-0.83]), interferon plus somatostatin analogue (HR, 0.31 [95% CI, 0.13-0.71]), somatostatin analogue (HR, 0.46 [95% CI, 0.33-0.66]), and sunitinib (HR, 0.42 [95% CI, 0.26-0.67]), and 5 therapies for gastrointestinal NETs: bevacizumab plus somatostatin analogue (HR, 0.22 [95% CI, 0.05-0.99]), everolimus plus somatostatin analogue (HR, 0.31 [95% CI, 0.11-0.90]), interferon plus somatostatin analogue (HR, 0.27 [95% CI, 0.07-0.96]), Lu 177–dotatate plus somatostatin analogue (HR, 0.08 [95% CI, 0.03-0.26], and somatostatin analogues (HR, 0.40 [95% CI, 0.21-0.78]) with higher efficacy than placebo and suggests an overall superiority of combination therapies.

CONCLUSIONS AND RELEVANCE The findings from this study suggest that a range of efficient therapies with different safety profiles is available for patients with NETs.

Invited Commentary
page 489

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Martin A. Walter, MD, Department of Nuclear Medicine, University Hospital, University of Geneva, Rue Gabrielle Perret-Gentil 4, 1205 Geneva, Switzerland (martin.walter@unige.ch).

JAMA Oncol. 2019;5(4):480-489. doi:10.1001/jamaoncol.2018.6720
Published online February 14, 2019.

The treatment of neuroendocrine tumors (NETs) is an interdisciplinary and dynamic field with many recent innovations from industry and academia. These successful treatments include the mechanistic target of rapamycin inhibitor everolimus,[1] the multitargeted receptor tyrosine kinase inhibitor sunitinib,[2] the vascular endothelial growth factor antibody bevacizumab,[3] the radiolabeled somatostatin analogue lutetium-177 (^{177}Lu)-dotatate,[4] and new combinations of previously established therapies.[5]

Several of these new therapies have demonstrated efficacy in randomized clinical trials (RCTs); however, translation of these results into widespread improved patient care faces several challenges. First, a therapeutic reference standard for treatment of NETs is lacking, and several therapies were compared only with placebo. Second, direct comparison of the most pertinent therapies is incomplete, complicating clinical decision making in selecting one therapy over another. Third, even though innovative and effective combinations of existing therapies have been developed in academic settings, they are often associated with a lack of representation in clinical guidelines.[6] We believe this systematic review and network meta-analysis of RCTs will satisfy the need for compiling and evaluating the available evidence on the safety and efficacy of NET therapies.

Key Points

Question What is the available evidence on therapies for neuroendocrine tumors?

Findings This systematic review and network meta-analysis identified 30 relevant randomized clinical trials comprising 3895 patients with neuroendocrine tumors assigned to 22 different therapies. A network meta-analysis identified 7 therapies for pancreatic neuroendocrine tumors and 5 therapies for gastrointestinal neuroendocrine tumors with a broad range of different toxic effects and higher efficacy than placebo.

Meaning There appears to be a range of efficient therapies with different safety profiles available for patients with neuroendocrine tumors.

Methods

The study was designed and conducted according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[7] The report was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement for systematic reviews[8,9] and its extension for network meta-analyses.[10]

Literature Search

We aimed to identify all RCTs comparing therapeutic interventions in NETs. In collaboration with Cochrane Switzerland, we developed a sensitive search algorithm using MeSH terms and text words in combination with an RCT filter (eTable 1 in the Supplement). Using this algorithm, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for studies reported from January 1, 1947, until March 2, 2018. We did not impose language or date restrictions or any exclusion criteria. In addition, we manually searched the trial registries ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch) for unpublished eligible trials. We then screened the abstracts from relevant meetings in 2017 and 2018, such as the annual conference of the American Society of Clinical Oncology, the North American Neuroendocrine Tumor Society (NANETS), and the European Neuroendocrine Tumor Society (ENETS), and searched the reference lists of included RCTs and relevant reviews. Key search terms included *neuroendocrine tumors*, *gastrointestinal neoplasms*, *therapy*, and *randomized controlled trial*.

Study Selection

For the qualitative analysis, we included RCTs comparing a therapeutic intervention with placebo or with an active therapeutic intervention in patients with NETs. For the quantitative analysis, we included all RCTs reporting disease control after 12 months and/or progression-free survival. Eight investigators (R.M.K., M.S., A.K., C.A.S., E.R.C., P.R., M.B., M.A.W.) working in duplicate independently screened titles and abstracts for potentially relevant studies. Five investigators (R.M.K., C.A.S., E.R.C., P.R., M.B.) working in duplicate and then independently screened the full-text report of all potentially relevant studies. Discordances were discussed with a third reviewer (M.A.W.) and resolved by consensus.

Outcomes and Data Extraction

Efficacy outcomes were disease control, progression-free survival, overall survival, and quality of life. Safety outcomes were nonserious and serious adverse events. If values for disease control rate were not available, we used the sum of the rates of complete response, partial response, and stable disease, or 100% minus the rate of disease progression. We extracted absolute values, hazard ratios (HRs), and 95% CIs for progression-free survival and overall survival. We also extracted data on sex, age, tumor type, tumor grading, metastases, functional tumors, follow-up duration, follow-up completeness, sample size calculation, study size, and industry sponsorship. Three investigators (R.M.K., M.S., A.K.) working in duplicate independently extracted all data. Discordances were discussed with a third reviewer (M.A.W.) and resolved by consensus. We contacted the corresponding authors of included RCTs to request additional information if needed, and we assessed the inclusion of RCTs in the recent pertinent guidelines.

Risk of Bias and Quality of Evidence

We assessed the risk of bias for all included RCTs with the Cochrane Risk of Bias Tool[7] and evaluated the quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[11,12] The details for these assessments are presented in the eMethods in the Supplement.

Statistical Analysis

We performed a network meta-analysis with a frequentist approach using the netmeta package[13,14] in R, version 3.5 .[15] We analyzed the end points disease control after 12 months and progression-free survival each for pancreatic NET (pNET) and

gastrointestinal NET (GI-NET). We applied a continuity correction for studies with a 0 cell count by adding 0.5 to all cell frequencies. We ranked therapies based on P scores, measuring the extent of certainty that a treatment is better than another, averaged over all competing therapies.[16]

If applicable, we assessed heterogeneity by the between-study-variance τ,[2] Cochran *Q* (weighted sum of squared differences between individual study effects and the pooled effect across studies), and I^2 (percentage of variation across studies due to heterogeneity rather than chance). If quantification of heterogeneity was not possible, we fitted fixed-effect models; otherwise, we used random-effects models. We assumed consistency for all networks but could not assess it completely owing to the low number of studies.

We quantified inconsistency by a net split analysis in which direct and indirect estimates were compared and a calculation of the between-design part of Cochran *Q* analysis. We summarized all results using forest plots with combined effect estimates (ie, odds ratios and HRs, 95% CIs, and size of boxes proportional to the inverse of the SEs).

Two RCTs[17,18] in the network meta-analysis did not report HRs. Although the number of events did not match the Kaplan-Meier curves in 1 RCT,[17] all reported events could be identified in the Kaplan-Meier curves of the other RCT.[18] We contacted the author teams of these trials but did not obtain further data. Thus, we estimated HRs for both RCTs from reconstructed curves by using a Cox proportional hazards regression model and by disregarding the given number of events not matching the Kaplan-Meier curves.[17] Two-tailed *P* values <.05 were considered to indicate statistical significance.

Results

Study Selection

We screened 3671 titles and abstracts and 150 full-text articles and found 38 relevant publications reporting 30 primary RCTs and 8 subgroup analyses (eFigure 1 in the Supplement). One of these primary RCTs[19] and 5 of these subgroup analyses,[20-25] with 1 reported in 2 studies,[23,24] were available solely as conference abstracts. A total of 16 RCTs reported disease control and/or progression-free survival and were included in the network meta-analyses. Many of the RCTs were reported in more than 1 publication.

Study Characteristics

The 30 relevant RCTs were conducted in 41 countries on 5 continents and were published between 1980 and 2018. Eleven RCTs included mainly GI-NETs, 9 included mainly pNETs, 8 included GI-NETs and pNETs, and 2 did not specify the type. Overall, 3895 patients were recruited; 22 different therapies were evaluated, including biotherapies, chemotherapies, targeted drugs, locoregional therapies, surgical treatment, and targeted radiopeptide therapy. Most of the 16 RCTs in the network meta-analysis were industry sponsored, and most of the 2944 included patients with metastatic NETs. Further characteristics of included RCTs and patients are provided in eTables 2 and 3 in the Supplement. The characteristics of RCTs and subgroup-analyses not in the network meta-analysis are reported in eTable 4 in the Supplement, and the characteristics of their respective patients are reported in eTable 5 in the Supplement.

Risk of Bias

Among 30 RCTs and 8 subgroup analyses, 20 had low risk for bias in random sequence generation (selection bias, 53%), 20 had low risk for bias in allocation concealment (selection bias, 53%), 21 had low risk for bias in blinding participants and personnel (performance bias, 55%), 19 had low risk for bias in blinding the outcome assessment (detection bias, 50%), 32 had low risk for bias of incomplete outcome data (attrition bias, 84%), and 32 had low risk for bias of selective reporting (reporting bias, 84%) (eTable 6 in the Supplement). Overall, 26 publications (68%) were free of high risk for bias in all of the above-mentioned domains.

Treatment Efficacy in pNETs

Eight RCTs compared disease control rates for 8 different therapies in pNETs (**Figure 1**A).[2,5,17,26-33] The network meta-analysis found that single therapy with everolimus and combination therapies were highly effective. Specifically, everolimus (P score, 0.82), everolimus plus a somatostatin analogue (P score, 0.73), and interferon plus a somatostatin analogue (P score, 0.71) achieved the highest disease control rates, followed by single treatment with interferon (P score, 0.62), somatostatin analogues (P score, 0.54), sunitinib (P score, 0.39), placebo (P score, 0.13), and dactolisib (P score, 0.06). All therapies except interferon, sunitinib, and dactolisib showed significantly higher disease control rates than placebo (Figure 1C; eFigure 2 in the Supplement).

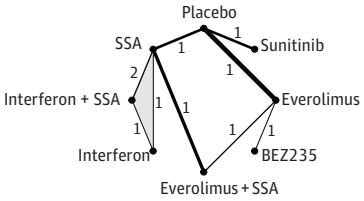
In addition, 8 RCTs (one 3-arm trial) assessed progression-free survival for 9 different therapies in pNETs (Figure 1B).[2,5,17,26-29,32-35] The network meta-analysis found that combination therapies were highly effective, with HRs between 0.31 and 0.35 vs placebo. The lowest hazard for progression was found after treatment with interferon plus a somatostatin analogue (P score, 0.77), followed by everolimus plus a somatostatin analogue (P score, 0.72), everolimus (P score, 0.72), interferon (P score, 0.62), sunitinib (P score, 0.51), everolimus plus bevacizumab plus a somatostatin analogue (P score, 0.44), somatostatin analogues (P score, 0.37), dactolisib (P score, 0.33), and placebo (P score, 0.01). All therapies but dactolisib significantly reduced the hazard for progression compared with placebo (Figure 1D; eFigure 3 in the Supplement). The quality of evidence in pNETs was generally the highest for comparisons including everolimus. The detailed results of the quality assessment are displayed in eTables 7 and 8 in the Supplement.

Treatment Efficacy in GI-NETs

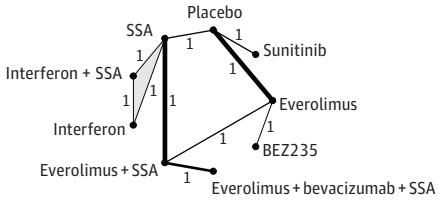
Ten RCTs assessed disease control rates for 9 different therapies in GI-NETs (**Figure 2**A).[1,5,17,18,26,30,31,36-40] Again, the network meta-analysis found that combination therapies were highly effective. Bevacizumab plus a somatostatin analogue resulted in the highest disease control rate (P score, 0.93), followed by ^{177}Lu-dotatate plus a somatostatin analogue (P score,

Figure 1. Treatment Efficacy in Pancreatic Neuroendocrine Tumors (pNETs)

A Network disease control in pNET



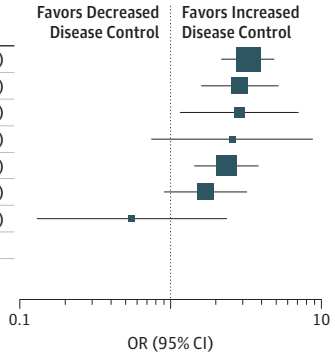
B Network PFS in pNET



C Disease control in pNET

Source	No./Total No. of Patients	GRADE Quality of Evidence	OR (95% CI)
Everolimus	247/319	4	3.29 (2.21-4.90)
Everolimus + SSA	248/295	4	2.89 (1.61-5.19)
Interferon + SSA	20/75	1	2.88 (1.16-7.13)
Interferon	8/23	1	2.58 (0.75-8.81)
SSA	260/387	2	2.36 (1.43-3.88)
Sunitinib	62/86	2	1.72 (0.91-3.27)
Dactolisib	28/31	1	0.56 (0.13-2.37)
vs Placebo	203/391		

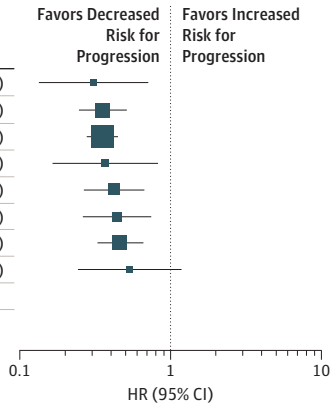
Subtotal τ^2 = not estimable; I^2 = not estimable; Cochran $Q = 1.11_2$; $P = .58$



D PFS in pNET

Source	Total No. of Patients	GRADE Quality of Evidence	HR (95% CI)
Interferon + SSA	21	2	0.31 (0.13-0.71)
Everolimus + SSA	370	4	0.35 (0.25-0.51)
Everolimus	319	4	0.35 (0.28-0.45)
Interferon	23	2	0.37 (0.16-0.83)
Sunitinib	86	3	0.42 (0.26-0.67)
Everolimus + bevacizumab + SSA	75	1	0.44 (0.26-0.75)
SSA	336	3	0.46 (0.33-0.66)
Dactolisib	31	1	0.54 (0.24-1.19)
vs Placebo	391		

Subtotal τ^2 = not estimable; I^2 = not estimable; Cochran $Q = 1.01_1$; $P = .91$



Network plots for disease control (A) and progression-free survival (PFS) (B) in pNETs. The thickness of the edges is proportional to the inverse SEs of the pairwise comparisons, and the numbers indicate the number of studies. One 3-arm study is marked by shading. C and D, Forest plots for disease control and PFS, respectively, in pNETs. The forest plots include only comparisons vs placebo. An odds ratio (OR) larger than 1 indicates increased disease control of the active treatment and a hazard ratio (HR) smaller than 1 indicates a reduced risk for progression for the active treatment. An HR smaller than 1 indicates a reduced risk for progression. All therapies are listed in order of their P scores, with the most effective therapy at the top. Heterogeneity was assessed by the between-study variance τ^2 value, Cochran Q with a P value, and I^2. Total No. refers to the total number of patients, and No. to the number of patients with disease control. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of estimates from pairwise and network meta-analysis, where 1 is very low; 2, low; 3, moderate; and 4, high. SSA indicates somatostatin analogue.

0.92), interferon plus a somatostatin analogue (P score, 0.66), everolimus plus a somatostatin analogue (P score, 0.53), interferon (P score, 0.52), somatostatin analogues (P score, 0.40), everolimus (P score, 0.39), placebo (P score, 0.12), and streptozocin plus fluorouracil (P score, 0.04). All therapies but interferon, everolimus, and streptozocin plus fluorouracil showed significantly higher disease control rates than placebo (Figure 2C; eFigure 4 in the Supplement).

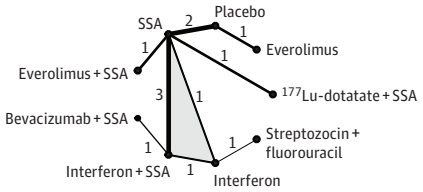
Eight RCTs assessed progression-free survival for 8 different therapies in GI-NETs (Figure 2B) and, again, the network meta-analysis found that combination therapies were highly effective, with HRs between 0.08 and 0.31 vs placebo.[1,3,5,17,18,26,31,36,37,40] The lowest hazard for progression was found after treatment with ^{177}Lu-dotatate plus a somatostatin analogue (P score, 0.97), followed by bevacizumab plus a somatostatin analogue (P score, 0.68), interferon plus a somatostatin analogue (P score, 0.59), everolimus plus a somatostatin analogue (P score, 0.53), interferon (P score, 0.50), somatostatin analogues (P score, 0.38), everolimus (P score, 0.33), and placebo (P score, 0.02). All therapies but interferon and everolimus significantly reduced the hazard for progression compared with placebo (Figure 2D; eFigure 5 in the Supplement). The quality of evidence in GI-NETs was generally the highest for comparisons including somatostatin analogues. The detailed results of the quality assessment are displayed in eTables 9 and 10 in the Supplement.

Disease Control, Progression-Free Survival, and Overall Survival

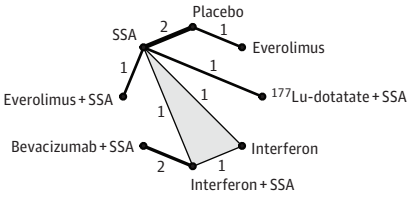
Twelve RCTs reported data on disease control and progression-free survival,[1,2,5,17,18,26-29,36,37,41] and both outcomes were generally positively associated (eFigure 6 in the Supplement).

Figure 2. Treatment Efficacy in Gastrointestinal Neuroendocrine Tumors (GI-NETs)

A Network disease control in GI-NET



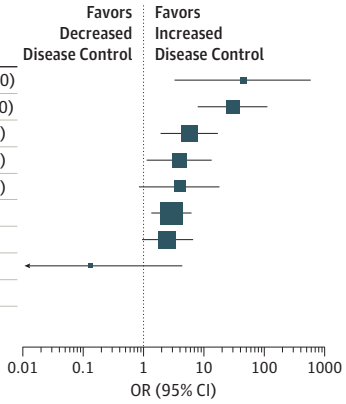
B Network PFS in GI-NET



C Disease Control in GI-NET

Source	No./Total No. of Patients	GRADE Quality of Evidence	OR (95% CI)
Bevacizumab + SSA	21/22	1	45.0 (3.32-609.00)
177Lu-dotatate + SSA	93/116	1	30.4 (8.19-113.00)
Interferon + SSA	63/130	1	5.71 (1.90-17.20)
Everolimus + SSA	187/216	1	3.97 (1.15-13.70)
Interferon	18/33	1	4.03 (0.86-18.80)
SSA	337/577	3	2.93 (1.36-6.32)
Everolimus	169/205	2	2.53 (0.95-6.79)
Streptozocin + fluorouracil	4/10	1	0.13 (0.00-4.58)
vs Placebo	124/243		

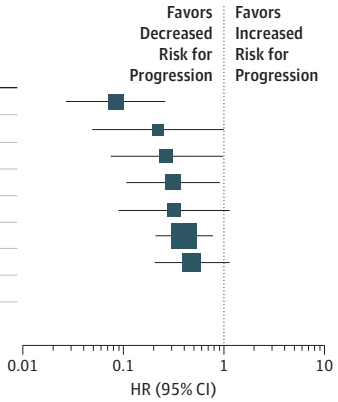
Subtotal $\tau^2 = 0.17$; $I^2 = 43.4\%$; Cochran $Q = 5.30_3$; $P = .15$



D PFS in GI-NET

Source	Total No. of Patients	GRADE Quality of Evidence	HR (95% CI)
177Lu-dotatate + SSA	116	1	0.08 (0.03-0.26)
Bevacizumab + SSA	222	1	0.22 (0.05-0.99)
Interferon + SSA	245	1	0.27 (0.07-0.96)
Everolimus + SSA	216	1	0.31 (0.11-0.90)
Interferon	23	1	0.32 (0.09-1.14)
SSA	491	2	0.40 (0.21-0.78)
Everolimus	205	1	0.48 (0.20-1.13)
vs Placebo	243		

Subtotal $\tau^2 = 0.16$; $I^2 = 58.8\%$; Cochran $Q = 4.86_2$; $P = .09$



Network plots for disease control (A) and progression-free survival (PFS) (B) in GI-NETs. The thickness of the edges is proportional to the inverse SEs of the pairwise comparisons, and the numbers indicate the number of studies. One 3-arm study is marked by shading. C and D, Forest plots for disease control and PFS, respectively, in GI-NET. The forest plots include only comparisons vs placebo. An odds ratio (OR) larger than 1 indicates increased disease control of the active treatment and a hazard ratio (HR) smaller than 1 indicates a reduced risk for progression for the active treatment. An HR smaller than 1 indicates a reduced risk for progression. All therapies are listed in order of their P scores, with the most effective therapy at the top. Heterogeneity was assessed by the between-study variance τ^2 value, Cochran Q with a P value, and I^2. Total No. refers to the total number of patients, and No. to the number of patients with disease control. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence of estimates from pairwise and network meta-analysis, where 1 is very low; 2, low; 3, moderate; and 4, high. 177Lu-dotatate indicates radiolabeled lutetium Lu 177-dotatate; SSA, somatostatin analogue.

Moreover, 11 RCTs reported data on overall survival (eTable 11 in the Supplement),[2,19,29,30,32-35,42-44] and 8 RCTs reported both progression-free survival and overall survival.[1-3,29,34,36,37,42] In each of these RCTs, superiority of a therapy regarding progression-free survival was associated with superiority regarding overall survival.

Quality of Life and Safety

Ten RCTs reported effects on quality of life,[1,2,26,30,31,33,35,36,40,42,44-48] and 7 of these quantified changes for 7 different therapies with the Quality of Life Questionnaire C30 of the European Organization for Research and Treatment of Cancer.[2,26,30,31,33,35,36,42,44-46] Of these, telotristat etiprate had the greatest effect on improving quality of life, followed by somatostatin analogues (eTable 12 in the Supplement). Furthermore, 12 RCTs and 7 subgroup analyses[1,26-29,31,32,37,39-42,45,46,49,50] reported frequencies of adverse events for 12 different therapies, of which dactolisib showed the highest and interferon plus a somatostatin analogue showed the lowest rates of serious adverse events (83.9% vs 3.0%) (**Table**). Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; grade 4, life-threatening).[51]

Representation in International Guidelines

Only 14 of the existing 30 RCTs and 8 subgroup analyses (37%) on NET treatment were included in both the latest NANETS and ENETS consensus guidelines (eTables 2 and 4 in the Supplement); thus, 63% were not included in both guidelines.

Table. Percentage of Patients With Adverse Events According to Treatment

Treatment	Grades, No./Total No. (%)[a]		Source, Reference No.
	3-4	All	
Dactolisib	26/31 (83.9)	31/31 (100)	28
Everolimus + somatostatin analogue	67/98 (68.4)	81/98 (82.7)	27, 41
Capecitabine + streptozocin + cisplatin	25/40 (62.5)	37/40 (92.5)	42
Everolimus	309/521 (59.3)	291/316 (92.1)	1, 27, 29, 31, 32, 40
Capecitabine + streptozocin	18/43 (41.9)	41/43 (95.3)	42
^{177}Lu-dotatate + somatostatin analogue	46/111 (41.4)	105/111 (94.6)	37
Hepatic arterial chemoembolization	3/12 (25.0)	11/12 (91.7)	49
Somatostatin analogue	72/344 (20.9)	226/324 (69.8)	26, 37, 39, 41, 45, 50
Placebo	92/480 (19.2)	278/363 (76.6)	26, 29, 32, 45, 46, 50
Hepatic arterial embolization	2/14 (14.3)	12/14 (85.7)	49
Interferon + somatostatin analogue	1/33 (3.0)	7/33 (21.2)	39
Telotristat	0	79/90 (87.8)	46

Abbreviation: ^{177}Lu-dotatate, radiolabeled lutetium Lu 177–dotatate.

[a] Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events: grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; and grade 4, life-threatening.

Specifically, 12 of 27 publications (44%) with industry sponsoring[1-3,5,17,26,29-33,35-37,40,46,49] and 2 of 11 publications (18%) without industry sponsoring[43,48] were included in both guidelines (eTables 2 and 4 in the Supplement).

Discussion

This systematic review identified 30 RCTs that randomized 3895 patients to 22 different therapies. To our knowledge, this represents the most comprehensive overview of the available safety and efficacy data for NET therapies, and its main findings can be summarized as follows.

First, the results suggest a superiority of combination therapies, especially of those including somatostatin analogues. In pNETs, somatostatin analogues plus interferon, everolimus, or everolimus plus bevacizumab were highly efficacious. The certainty of evidence for these therapies was variable and was the highest for somatostatin analogues plus everolimus. In GI-NETs, somatostatin analogues plus ^{177}Lu-dotatate, bevacizumab, interferon, or everolimus were highly efficacious. Also, the certainty of evidence for these therapies was variable and was highest for somatostatin analogues plus ^{177}Lu-dotatate.

Second, the results suggest a range of monotherapies that are superior to placebo, including everolimus, interferon, and sunitinib in pNETs, and somatostatin analogues in pNETs and GI-NETs. Conversely, the results did not demonstrate efficacy superior to that of placebo for dactolisib in pNETs or for interferon or everolimus in GI-NETs. The highest quality of evidence was available for everolimus in pNETs, alone or in combination with somatostatin analogues.

Third, the results indicate that NET therapies have a broad range of risk for adverse events and effects on quality of life. Because systemic treatment is commonly noncurative for NETs, adverse events and quality of life are priorities. The results of this study may help to put the available safety data for NET therapies into perspective. The findings may guide treatment choice, initiate preventive measures, and result in increased patient surveillance. In addition, they demonstrate the need for more research in assessing adverse events and effects on quality of life for NET therapies.

Strengths and Limitations

This study has limitations. We conducted a comprehensive literature search with a sensitive search algorithm and an extensive manual search of reference lists and conference proceedings. We therefore consider it unlikely that we missed relevant RCTs. However, we could not obtain additional unpublished data and are aware that a substantial amount of information is not available to the public. Thus, we cannot rule out publication bias.

When using the available information for therapeutic decisions in treatment of NETs, we propose to consider the following points regarding indirectness, transitivity, risk of bias, inconsistency, incoherence, and imprecision. First, meta-analyses are based on the assumption of directness, in which populations, therapies, and outcomes of included studies are aligned with population, therapies, and outcomes targeted by the meta-analysis. Our meta-analysis targeted all available therapies and included only studies reporting disease control and/or progression-free survival. Both factors ensured a certain degree of directness. Yet, indirectness was introduced by RCTs including mixed populations of patients with pNETs and GI-NETs. We highlight all comparisons that were affected by indirectness (eTables 4-7 in the Supplement) to allow incorporation of this fact into clinical decision making.

Second, network meta-analyses are also based on the assumption of transitivity, in which the included studies are similar enough to build a network. In this study, the well-defined populations and outcomes resulted in a network with high overall transitivity. Yet, the different types of interferons[3,17,18,30,38,39] and somatostatin analogues[3,5,17,18,26,27,30,31,36,37,39] introduced intransitivity for the loop of comparisons of interferon, somatostatin analogues, and their combination, but had no association with the certainty of evidence for the rest of the network.

Third, some RCTs had a high risk of bias due to absent blinding, including the RCTs evaluating the 3 most efficacious therapies in GI-NETs: somatostatin analogues plus bevacizumab,[3,18] plus ^{177}Lu-dotatate,[37] or plus interferon.[17] Absent blinding has been shown to be associated with an average exaggeration of estimated therapeutic effects of approximately 9%.[52] However, the therapeutic effect for the 3 aforementioned therapies compared with placebo substantially exceeds 9% and they most likely represent the superior therapies in GI-NETs, although the extent of superiority needs to be interpreted with caution.

Fourth, consistency describes the agreement between estimates of different studies for a specific comparison, while coherence describes agreement between direct and indirect estimates for a specific comparison. Owing to the relatively low number of RCTs, the assessment of incoherence and inconsistency was limited. We identified 6 comparisons in which indirect and direct estimates differed considerably, without being statistically significant, and 2 cases of inconsistency. Two RCTs compared somatostatin analogues with placebo,[26,36] and 3 RCTs compared somatostatin analogues with somatostatin analogues plus interferon.[17,30,39] Likely owing to different types of somatostatin analogues and interferons, the RCTs found different effects regarding disease control and progression-free survival.

Fifth, the low number of RCTs compared with the number of interventions induced imprecision to several comparisons, manifesting as wide 95% CIs that include or are close to a null effect. A statistically significant effect does not automatically represent a clinically relevant effect, and the consequence of imprecision is that wide 95% CIs might include significant but clinically irrelevant effects. As clinical relevance often depends on an individual patient's situation, we highlighted all comparisons that were affected by imprecision (eTables 4-7 in the Supplement) to allow incorporation of this fact into clinical decision making.

We used the GRADE system to assess the confidence in effect estimates for all comparisons, depending on indirectness, transitivity, risk of bias, inconsistency, incoherence, and imprecision. We incorporated the certainty of evidence in the main results of our analysis (eTables 4-7 in the Supplement) to highlight the most robust findings for further use in clinical judgment.

Sixth, we used the end points disease control and progression-free survival for all network analyses, instead of overall survival. Although overall survival is arguably the most relevant clinical end point, it is used less frequently because it requires a larger number of patients and longer follow-up. Use of overall survival also prevents crossover trial designs and might be confounded by the effect of salvage therapies used after disease progression.[53] In NETs, progression-free survival has been shown to be well correlated with overall survival,[54] and the RCTs included in the present study revealed the same correlation. Using disease control and progression-free survival instead of overall survival in this study allowed including more therapies into the network meta-analyses, which we believe represents the preferred approach.

Implications

Our results have implications for clinicians, guideline committees, and researchers. First, clinical decisions should be based on the best available evidence. The present results provide a comprehensive overview of the existing evidence on NET therapies as well as the best possible comparison of therapies that have not been directly compared in RCTs. Using this approach, the certainty of evidence is incorporated into the results to assist in decision making. Safety and efficacy results should both be incorporated into the treatment decision, while in addition the safety results may aid in the decision to establish preventive measures and increase the surveillance for known toxic effects.

Furthermore, the results support the adaption of clinical guidelines. Although there is no requirement to incorporate all evidence from RCTs into clinical guidelines, this systematic review presents an overview of the existing evidence from which guideline makers can choose. For example, evidence from RCTs on alosetron,[55] dactolisib,[28] capecitabine,[42] temozolomide,[19] and surgical ligation devices[56] in NETs has not been integrated into many guidelines, and combination therapies could be better represented. Everolimus plus a somatostatin analogue showed high efficacy in pNETs and is widely recommended only by the Carcinoid-Neuroendocrine Tumor Society Canada.[57] It is recommended solely for functionally active pNETs by the ENETS, but not by the NANETS.[58,59] Interferon plus a somatostatin analogue showed high efficacy and low toxic effects in pNETs and is recommended for pNETs with reservation by the ENETS, but not by NANETS.[58,59] Conversely, ^{177}Lu-dotatate plus a somatostatin analogue showed high efficacy in GI-NETs and is recommended by the NANETS, but not by the ENETS.[58,60] Bevacizumab plus a somatostatin analogue showed high efficacy in GI-NET, but is not recommended by either the NANETS or ENETS.[58,60]

Similarly, NET guidelines by the European Society for Medical Oncology,[61] National Comprehensive Cancer Network,[62] Scottish Neuroendocrine Tumour Group,[63] and UK and Ireland Neuroendocrine Tumour Society[64] do not recommend combinations of everolimus, interferon, bevacizumab, or ^{177}Lu-dotatate plus a somatostatin analogue. Yet, the Scottish Neuroendocrine Tumour Group guidelines mention possible benefits of bevacizumab or everolimus plus a somatostatin analogue in pNET.[63]

The present results may guide future research by highlighting necessary head-to-head comparisons and facilitating their trial design.[65] Specifically, dactolisib and everolimus plus bevacizumab plus a somatostatin analogue have only been compared with 1 other active therapy in pNET yet, while everolimus, everolimus plus a somatostatin analogue, bevacizumab plus a somatostatin analogue, ^{177}Lu-dotatate plus a somatostatin analogue, and streptozocin plus fluorouracil have only been compared with 1 other active therapy in GI-NETs. Sunitinib and everolimus have been compared only with placebo in pNETs and GI-NETs respectively, and, to our knowledge, head-to-head comparisons with active therapies in RCTs have not yet been performed. When designing such head-to-head comparisons, the estimated associations from our network meta-analysis can help

to select the reference therapy and approximate the required patient numbers. Particularly, because the present results identified 7 therapies in pNETs and 5 therapies in GI-NETs with higher efficacy than placebo, comparisons with placebo as a reference are discouraged for the future. Because of their proven efficacy and central role in current comparisons, somatostatin analogues represent the logical reference compound for further RCTs. Moreover, the quality assessment of currently available RCTs revealed that further studies should incorporate blinding to avoid overestimation of effects and improve the overall quality of evidence in the field.

Conclusions

Herein, we present a systematic review and network meta-analysis of available RCTs evaluating the safety and efficacy of therapies for NETs. This overview of what we believe to be the most pertinent and current evidence demonstrates a range of efficient therapies with different safety profiles that are available for patients with NETs and may facilitate informed clinical decision making, drafting of guidelines, and planning of future research.

ARTICLE INFORMATION

Accepted for Publication: November 26, 2018.

Published Online: February 14, 2019. doi:10.1001/jamaoncol.2018.6720

Author Affiliations: Department of Visceral Surgery and Medicine, Bern University Hospital, University of Bern, Bern, Switzerland (Kaderli, Seiler); Department of Nuclear Medicine, University Hospital, University of Geneva, Geneva, Switzerland (Spanjol, Gloy, Dumont, Radojewski, Walter); Department of Medical Oncology, Bern University Hospital, University of Bern, Bern, Switzerland (Kollár); Clinical Trials Unit Bern, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Bütikofer); Department of Endocrinology, Diabetes, and Metabolism, Basel University Hospital, University of Basel, Basel, Switzerland (Christ); Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, Basel University Hospital, University of Basel, Basel, Switzerland (Briel); Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada (Briel).

Author Contributions: Drs Kaderli and Walter had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kaderli, Seiler, Radojewski, Briel, Walter.
Acquisition, analysis, or interpretation of data: Kaderli, Spanjol, Kollar, Bütikofer, Gloy, Dumont, Seiler, Christ, Radojewski, Walter.
Drafting of the manuscript: Kaderli, Spanjol, Bütikofer, Dumont, Radojewski, Walter.
Critical revision of the manuscript for important intellectual content: Kaderli, Spanjol, Kollar, Bütikofer, Gloy, Dumont, Seiler, Christ, Briel, Walter.
Statistical analysis: Bütikofer, Gloy, Walter.
Obtained funding: Kaderli, Radojewski, Walter.
Administrative, technical, or material support: Spanjol, Dumont, Walter.
Supervision: Seiler, Christ, Briel, Walter.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded by the Insula Stiftung zur Förderung der viszeralchirurgischen Forschung.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Erik von Elm, MD, and Thomas Brauchli of (Cochrane Switzerland) assisted with the electronic libraries search, and Samira Sadowski, MD (University of Geneva), and Aurel Perren, MD (University of Bern) provided valuable input on the manuscript. No compensation was received for these contributions.

REFERENCES

1. Yao JC, Fazio N, Singh S, et al; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016; 387(10022):968-977. doi:10.1016/S0140-6736(15)00817-X

2. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6): 501-513. doi:10.1056/NEJMoa1003825

3. Yao JC, Guthrie KA, Moran C, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. *J Clin Oncol*. 2017;35(15):1695-1703. doi:10.1200/JCO.2016.70.4072

4. Strosberg JR, Wolin EM, Chasen B, et al. NETTER-1 phase III: Progression-free survival, radiographic response, and preliminary overall survival results in patients with midgut neuroendocrine tumors treated with 177-Lu-dotatate. *J Clin Oncol*. 2016;34(4)(suppl): 194-194. doi:10.1200/jco.2016.34.4_suppl.194

5. Pavel ME, Hainsworth JD, Baudin E, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012. doi:10.1016/S0140-6736(11)61742-X

6. Boudoulas KD, Leier CV, Geleris P, Boudoulas H. The shortcomings of clinical practice guidelines. *Cardiology*. 2015;130(3):187-200. doi:10.1159/000371572

7. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. http://handbook.cochrane.org. Updated September 2018. Accessed January 8, 2019.

8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, W64.

9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-W94. doi:10.7326/0003-4819-151-4-200908180-00136

10. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015; 162(11):777-784. doi:10.7326/M14-2385

11. Puhan MA, Schünemann HJ, Murad MH, et al; GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ*. 2014; 349:g5630. doi:10.1136/bmj.g5630

12. Brignardello-Petersen R, Bonner A, Alexander PE, et al; GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *J Clin Epidemiol*. 2018;93:36-44. doi:10.1016/j.jclinepi.2017.10.005

13. Schwarzer G, Carpenter JR, Rücker G. *Meta-Analysis with R (Use R!)*. Geneva, Switzerland: Springer; 2015. doi:10.1007/978-3-319-21416-0

14. Rücker G, Schwarzer G, Krahn U, König J. netmeta: Network Meta-Analysis using Frequentist Methods. 2017; R-Package version 0.9-7. https://cran.r-project.org/web/packages/netmeta/index.html. Accessed January 1, 2018.

15. Al-Qahtani KH, Tunio MA, Asiri MA, et al. Comparative clinicopathological and outcome analysis of differentiated thyroid cancer in Saudi patients aged below 60 years and above 60 years. *Clin Interv Aging*. 2016;11:1169-1174. doi:10.2147/CIA.S107881

16. Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*. 2015; 15:58. doi:10.1186/s12874-015-0060-8

17. Faiss S, Pape UF, Böhmig M, et al; International Lanreotide and Interferon Alfa Study Group. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors—the International Lanreotide and Interferon Alfa Study Group. *J Clin Oncol*. 2003;21 (14):2689-2696. doi:10.1200/JCO.2003.12.142

18. Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol*. 2008; 26(8):1316-1323. doi:10.1200/JCO.2007.13.6374

19. Kunz PL, Catalano PJ, Nimeiri H, et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). *J Clin Oncol*. 2018;36(15)(suppl):4004.

20. Phan AT, Caplin ME, Pavel ME, et al. Effects of lanreotide autogel/depot (LAN) in pancreatic neuroendocrine tumors (pNETs): a subgroup analysis from the CLARINET study. *J Clin Oncol*. 2015;33(3)(suppl):233.

21. Phan AT, Caplin ME, Pavel ME, et al. Effects of lanreotide autogel/depot (LAN) in patients with neuroendocrine tumors (NETs) age 65 or younger versus older than age 65: subgroup analyses from the CLARINET study. *J Clin Oncol*. 2015;33(3)(suppl):36.

22. Dasari A, Phan AT, Caplin ME, et al. Lanreotide depot/autogel (LAN) in midgut neuroendocrine tumors (NETs): a subgroup analysis from the CLARINET study. *J Clin Oncol*. 2015;33(15)(suppl):4104. doi:10.1200/jco.2015.33.15_suppl.e15177

23. Fisher GA, Wolin EM, Kunz P, et al. Safety and efficacy of lanreotide depot versus placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy. *Am J Gastroenterol*. 2015;110(suppl 1):1007.

24. Fisher GA, Wolin EM, Kunz P, et al. Efficacy and safety of lanreotide depot vs placebo in patients with neuroendocrine tumor and a history of carcinoid syndrome and prior octreotide therapy. *Pancreas*. 2016;45(3):475.

25. Anselmo L, Shaheen M, Casellini C, et al. Safety and efficacy of lanreotide depot vs placebo in neuroendocrine tumor patients with a history of carcinoid syndrome and prior octreotide therapy. *J Oncol Pharm Pract*. 2016;22(2)(suppl 1):19-20.

26. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233. doi:10.1056/NEJMoa1316158

27. Kulke MH, Ruszniewski P, Van Cutsem E, et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. *Ann Oncol*. 2017;28(6):1309-1315. doi:10.1093/annonc/mdx078

28. Salazar R, Garcia-Carbonero R, Libutti SK, et al. Phase II study of BEZ235 versus everolimus in patients with mammalian target of rapamycin inhibitor-naive advanced pancreatic neuroendocrine tumors. *Oncologist*. 2018;23(7):766-e90.

29. Yao JC, Shah MH, Ito T, et al; RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523. doi:10.1056/NEJMoa1009290

30. Arnold R, Rinke A, Klose KJ, et al. Octreotide versus octreotide plus interferon-alpha in endocrine gastroenteropancreatic tumors: a randomized trial. *Clin Gastroenterol Hepatol*. 2005;3(8):761-771. doi:10.1016/S1542-3565(05)00481-7

31. Phan AT, Dasari A, Liyanage N, Cox D, Pitman Lowenthal S, Wolin EM. Tumor response in the CLARINET study of lanreotide depot vs placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). J Clin Oncol. 2016;34(4 suppl):434. doi:10.1200/jco.2016.34.4_suppl.434

32. Yao JC, Pavel M, Lombard-Bohas C, et al. Everolimus for the treatment of advanced pancreatic neuroendocrine tumors: overall survival and circulating biomarkers from the randomized, phase III RADIANT-3 Study. *J Clin Oncol*. 2016;34(32):3906-3913. doi:10.1200/JCO.2016.68.0702

33. Vinik A, Bottomley A, Korytowsky B, et al. Patient-reported outcomes and quality of life with sunitinib versus placebo for pancreatic neuroendocrine tumors: results from an international phase III trial. *Target Oncol*. 2016;11(6):815-824. doi:10.1007/s11523-016-0462-5

34. Kulke MH, Niedzwiecki D, Foster NR, et al. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (alliance). *Pancreas*. 2016;45(3):477.

35. Faivre S, Niccoli P, Castellano D, et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Ann Oncol*. 2017;28(2):339-343.

36. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663. doi:10.1200/JCO.2009.22.8510

37. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135. doi:10.1056/NEJMoa1607427

38. Oberg K, Norheim I, Alm G. Treatment of malignant carcinoid tumors: a randomized controlled study of streptozocin plus 5-FU and human leukocyte interferon. *Eur J Cancer Clin Oncol*. 1989;25(10):1475-1479. doi:10.1016/0277-5379(89)90107-7

39. Kölby L, Persson G, Franzén S, Ahrén B. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg*. 2003;90(6):687-693. doi:10.1002/bjs.4149

40. Pavel ME, Singh S, Strosberg JR, et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(10):1411-1422. doi:10.1016/S1470-2045(17)30471-0

41. Castellano D, Bajetta E, Panneerselvam A, et al; RADIANT-2 Study Group. Everolimus plus octreotide long-acting repeatable in patients with colorectal neuroendocrine tumors: a subgroup analysis of the phase III RADIANT-2 study. *Oncologist*. 2013;18(1):46-53. doi:10.1634/theoncologist.2012-0263

42. Meyer T, Qian W, Caplin ME, et al. Capecitabine and streptozocin ± cisplatin in advanced gastroenteropancreatic neuroendocrine tumours. *Eur J Cancer*. 2014;50(5):902-911. doi:10.1016/j.ejca.2013.12.011

43. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. *N Engl J Med*. 1992;326(8):519-523. doi:10.1056/NEJM199202203260804

44. Meyer T, Qian W, Valle JW, et al. Capecitabine and streptozocin ± cisplatin for gastroenteropancreatic neuroendocrine tumours: predictors of long-term survival in the NET01 trial. *Ann Oncol*. 2016;27(suppl 6):vi136-vi148. doi:10.1093/annonc/mdw369.31

45. Vinik AI, Wolin EM, Liyanage N, Gomez-Panzani E, Fisher GA; ELECT Study Group. Evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment (ELECT): a randomized, double-blind, placebo-controlled trial. *Endocr Pract*. 2016;22(9):1068-1080. doi:10.4158/EP151172.OR

46. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35(1):14-23. doi:10.1200/JCO.2016.69.2780

47. Jacobsen MB, Hanssen LE. Clinical effects of octreotide compared to placebo in patients with gastrointestinal neuroendocrine tumours: report on a double-blind, randomized trial. *J Intern Med*. 1995;237(3):269-275. doi:10.1111/j.1365-2796.1995.tb01175.x

48. O'Toole D, Ducreux M, Bommelaer G, et al. Treatment of carcinoid syndrome: a prospective crossover evaluation of lanreotide versus octreotide in terms of efficacy, patient acceptability, and tolerance. *Cancer*. 2000;88(4):770-776. doi:10.1002/(SICI)1097-0142(20000215)88:4<770::AID-CNCR6>3.0.CO;2-0

49. Maire F, Lombard-Bohas C, O'Toole D, et al. Hepatic arterial embolization versus chemoembolization in the treatment of liver metastases from well-differentiated midgut endocrine tumors: a prospective randomized study. *Neuroendocrinology*. 2012;96(4):294-300. doi:10.1159/000336941

50. Oberg K, Norheim I, Theodorsson E, Ahlman H, Lundqvist G, Wide L. The effects of octreotide on basal and stimulated hormone levels in patients with carcinoid syndrome. *J Clin Endocrinol Metab*. 1989;68(4):796-800. doi:10.1210/jcem-68-4-796

51. US Dept of health and human services: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed January 8, 2019.

52. Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol*. 2007;36(4):847-857. doi:10.1093/ije/dym087

53. Saad ED, Buyse M. Statistical controversies in clinical research: end points other than overall survival are vital for regulatory approval of anticancer agents. *Ann Oncol*. 2016;27(3):373-378. doi:10.1093/annonc/mdv562

54. Imaoka H, Sasaki M, Takahashi H, et al. Progression-free survival as a surrogate endpoint in

advanced neuroendocrine neoplasms. *Endocr Relat Cancer*. 2017;24(9):475-483. doi:10.1530/ERC-17-0197

55. Saslow SB, Scolapio JS, Camilleri M, et al. Medium-term effects of a new 5HT3 antagonist, alosetron, in patients with carcinoid diarrhoea. *Gut*. 1998;42(5):628-634. doi:10.1136/gut.42.5.628

56. Sakata H, Iwakiri R, Ootani A, et al. A pilot randomized control study to evaluate endoscopic resection using a ligation device for rectal carcinoid tumors. *World J Gastroenterol*. 2006;12(25):4026-4028. doi:10.3748/wjg.v12.i25.4026

57. Singh S, Asa SL, Dey C, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: an evidence-based Canadian consensus. *Cancer Treat Rev*. 2016;47:32-45. doi:10.1016/j.ctrv.2016.05.003

58. Pavel M, O'Toole D, Costa F, et al; Vienna Consensus Conference participants. ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103(2):172-185. doi:10.1159/000443167

59. Kunz PL, Reidy-Lagunes D, Anthony LB, et al; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas*. 2013;42(4):557-577. doi:10.1097/MPA.0b013e31828e34a4

60. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society consensus guidelines for surveillance and medical management of midgut neuroendocrine tumors. *Pancreas*. 2017;46(6):707-714. doi:10.1097/MPA.0000000000000850

61. Öberg K, Knigge U, Kwekkeboom D, Perren A; ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;23(suppl 7):vii124-vii130.

62. Shah MH, Kulke MH, Goldner WS, et al. Neuroendocrine tumors, version 3.2018. NCCN Clinical Practice Guidelines in Oncology 2018; https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed October 06, 2018, 2018.

63. Bouvier C, Bradshaw N, Chong P, et al. Consensus guidelines for the management of patients with neuroendocrine tumors (v.1.1). http://www.woscan.scot.nhs.uk/wp-content/uploads/FINAL-PUBLISHED-SCONET-Guideline-v1.1-July-2015.pdf. Updated July 2015. Accessed February 15, 2018, 2018.

64. Ramage JK, Ahmed A, Ardill J, et al; UK and Ireland Neuroendocrine Tumour Society. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut*. 2012;61(1):6-32. doi:10.1136/gutjnl-2011-300831

65. Salanti G, Nikolakopoulou A, Sutton AJ, et al. Planning a future randomized clinical trial based on a network of relevant past trials. *Trials*. 2018;19(1):365. doi:10.1186/s13063-018-2740-2

Invited Commentary

Evaluating Risks and Benefits of Evolving Systemic Treatments of Neuroendocrine Tumors

Jonathan Raphael Strosberg, MD; Taymeyah Al-Toubah, MPH; Mauro Cives, MD

In recent years, the number of treatments for metastatic, well-differentiated gastrointestinal and pancreatic neuroendocrine tumors (NETs) has expanded significantly.[1] New medications for tumor control as well as symptom control include somatostatin analogues, everolimus, sunitinib, telotristat, and lutetium Lu 177 (^{177}Lu)-dotatate. These new therapies have been approved based on randomized clinical trials—an effort that has required international cooperation given the relative scarcity of metastatic NETs.

Related article page 480

With the introduction of new therapies, the problem of treatment sequencing has arisen. Most studies in the NET field have compared new treatments with a placebo or with a comparator of unknown efficacy (eg, high-dose octreotide in the Neuroendocrine Tumors Therapy (NETTER-1) registration trial for ^{177}Lu-dotatate).[2] Hence, it is difficult to compare various active therapies and contrast benefits and risks. To try to compare evidence across trials, Kaderli et al[3] embarked on a systematic review and network meta-analysis of randomized clinical trials. Their goal was to compare disease control, progression-free survival, overall survival, toxic effects, and quality of life across trials, assigning a P score, which measures the extent of certainty that one treatment is superior to another, averaged over all competing therapies.

In this analysis, the authors faced challenges that are more pertinent to the NET field than to most other cancers. First and foremost, NETs are clinically and biologically heterogeneous tumors. Some trials have evaluated midgut NETs, others have evaluated pancreatic NETs, and yet others have investigated gastroenteropancreatic NETs as a whole, with no clear breakdown of outcomes in specific subtypes. As a result, it is almost impossible to compare outcomes among different trials. Other complicating factors include use of different response criteria (eg, Response Evaluation Criteria in Solid Tumors vs World Health Organization) across different trials, heterogeneous radiographic analysis (local vs central review), as well as diverse baseline eligibility criteria (eg, progressive disease at baseline or not). Thus, we encounter situations in which median progression-free survival in the placebo arm of one trial is 6 months (PROMID study[4]: octreotide vs placebo) vs 18 months in the placebo arm of another (CLARINET study[5]: lanreotide vs placebo). Because transitivity is one of the main assumptions of network meta-analyses, as explained by Kaderli et al,[3] one may wonder whether this concept pertains to NET trials.

Another problem is that the quality of the trials has varied significantly over time. Early trials of interferon were substantially underpowered and nonblinded. This limitation has complicated interpretation of subsequent trials, such as Southwest Oncology Group S0518,[6] in which interferon was a control arm. Was bevacizumab, which performed no better than interferon, an active drug in high-risk NETs or not? The answer depends on the extent to which interferon is considered an effective treatment.

The question of combination vs sequential therapy cannot be addressed easily in this meta-analysis. Outcomes of combination treatment are often superior but fail to answer the fundamental question of whether treatments should be ad-